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Use of Tuberculosis Genotyping for Post-Outbreak Monitoring

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Abstract

Context—Review of routinely collected tuberculosis genotyping results following a known outbreak is a potential mechanism to examine the effectiveness of outbreak control measures.

Objective—Assess differences in characteristics between outbreak and post-outbreak tuberculosis cases.

Design—Retrospective

Setting—United States

Participants—All tuberculosis cases identified as a result of ≥5-person outbreaks investigated by the Centers for Disease Control and Prevention during 2003–2007 (original outbreak cases), and subsequent culture-positive TB cases with matching *M. tuberculosis* genotypes reported in the same county during 2004–2008 (post-outbreak cases).

Main Outcome Measure—Proportion of demographic, social, and clinical characteristics of tuberculosis outbreak cases compared to post-outbreak cases. Secondary: Proportion of demographic, social, and clinical characteristics of epidemiologically linked versus nonlinked cases.

Results—Six outbreaks with 111 outbreak cases and 110 post-outbreak cases were identified. Differences between outbreak and post-outbreak cases were gender (69% male versus 85%; $p<0.01$), birth origin (3% foreign-born versus 11% ; $p=0.02$), disease severity (48% sputum smear-positive versus 62%; $p=0.04$), homelessness (38% versus 51%; $p=0.05$), and injection drug use (4% versus 11%; $p=0.04$). For five of the six outbreaks, the status of epidemiologic relationships among post-outbreak cases was available (n=89). The post-outbreak cases with a known epidemiologic link to the original outbreak were in younger persons (age 39 versus 47; $p<0.01$), and a larger proportion reported injection drug use (18% versus 4%; $p=0.04$) or noninjection drug use (44% versus 18%; $p<0.01$) than those without a reported link.

Conclusions—Health jurisdictions can utilize genotyping data to monitor and define the characteristics of post-outbreak cases related to the original outbreak.

Keywords

Tuberculosis; Genotype; Population Surveillance; Public Health

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BACKGROUND

The causative agent of tuberculosis (TB), *Mycobacterium tuberculosis*, is spread through the air from person to person. *M. tuberculosis* genotyping has been used for more than a decade to study the epidemiology of TB, identify and monitor TB outbreaks, and describe risk factors associated with transmission.[1–5] Genotyping can help distinguish TB cases involved in the same chain of disease transmission by confirming suspected relationships and identifying potential new ones.

Approximately 80% of reported TB cases in the United States each year are diagnosed via microbial culture (culture positive); only culture-positive cases can be genotyped.[6] With the Centers for Disease Control and Prevention (CDC)'s establishment of the National Tuberculosis Genotyping Service (NTGS) in 2004, TB genotyping for each culture-positive TB case in the United States is available at no cost to patients, healthcare providers, or health departments.[7] Results are available to the TB control program that submits the case's *M. tuberculosis* isolate and to the state health department of that jurisdiction. For the initial 2004–2007 NTGS period, genotyping results were available for approximately 66% of all culture-positive TB cases in the United States.[8] By 2009, that percentage was approximately 81%; the goal is to achieve universal genotyping (100%).

Beginning in 2010, state and local TB control programs gained access to their genotyping results via a secure online platform, the TB Genotyping Information Management System (TB GIMS), where each case with NTGS results is linked with its corresponding National Tuberculosis Surveillance System (NTSS) case report.[6,8,9] TB GIMS has the potential to provide near real-time epidemiologic data to TB control programs, which can use this information to improve TB control by examining the effectiveness of interventions, such as case treatment and contact investigation, to halt chains of transmission.[9]

As one approach to identify additional outbreak-related cases after experiencing an outbreak, TB control programs can monitor genotyping results in their jurisdiction to see if the outbreak genotype recurs. Such a review of routine TB genotyping results is a potential mechanism to examine the effectiveness of outbreak control measures. To examine how genotyping information might enhance post-outbreak monitoring, our study compared characteristics of TB cases identified during known outbreaks to later cases with matching TB genotypes.

DESIGN

Participants, definitions, and data collection

Included in this analysis were case data from TB outbreaks investigated by CDC through onsite assistance during 2003–2007 where there were ≥5 cases with matching TB genotypes in a single U.S. county. Genotyping results were provided by the NTGS, which uses standard molecular characterization methods.[10] A matching genotype was defined as identical spoligotype and 12-locus mycobacterial interspersed repetitive unit variable number tandem repeats (MIRU-VNTR) results between cases.

The beginning of the outbreak was defined by the health jurisdiction seeking assistance, as reported in the letter of invitation to CDC. For the purposes of this analysis, the end of each outbreak was defined as the conclusion of CDC onsite assistance, which coincided with the end of the most intensive part of the investigation.

Within each CDC investigation, an outbreak case was defined as either having a matching genotype to, or, in the absence of genotype results (e.g., clinically diagnosed, culture-negative case), an epidemiologic link with, another outbreak case. An epidemiologic link was defined as being in the same location at the same time, as verified by record review or personal communication. In addition, outbreak cases were required to occur between the beginning and the end of the outbreak as defined above. Non-outbreak cases were all other TB cases reported by that county during the outbreak period.

A post-outbreak case was any TB case that occurred subsequent to the end of the outbreak (as defined above) in the same county where the outbreak occurred whose genotype matched the outbreak genotype. For this analysis, the post-outbreak investigation period encompassed 2004–2008, thus ranging from 1 to 5 years after each outbreak investigation. For post-outbreak cases, we attempted to ascertain epidemiologic relationships to the original outbreak through follow-up discussions with local and state TB control programs in those jurisdictions.

Demographic, social, and clinical characteristics for all cases were abstracted from NTSS records maintained at CDC. The month and year that health jurisdictions counted cases for surveillance purposes was used as a proxy for diagnosis date, which is not captured in the NTSS.

Statistical analysis and outcome measures

The NTSS provided an enumeration of all TB cases reported in each county during the defined outbreak period. Chi-square tests were used to determine whether outbreak cases were more likely than non-outbreak cases to have *M. tuberculosis* isolates submitted for genotyping. We then compared characteristics of outbreak to post-outbreak cases, and, among post-outbreak cases, compared the epidemiologically linked with the nonlinked cases. Fisher's exact tests were used when cell sizes for any variable were 5 or fewer. Wilcoxon nonparametric tests and t-tests were performed to determine whether the distributions of median or mean age differed between outbreak and post-outbreak cases. A 2-way contingency table analysis tool available at http://statpages.org/ctab2×2.html and SAS version 9.1.3 (SAS Institute) were used to perform analyses. A p-value of <=0.05 was considered significant.

RESULTS

Six outbreaks investigated by CDC during the study period met our inclusion criteria. In the six affected counties, 81% of all outbreak cases had isolates submitted for genotyping versus 66% of non-outbreak cases (p=0.01).

Outbreak versus post-outbreak cases

We identified a total of 111 outbreak cases and 110 post-outbreak cases. For post-outbreak cases, the mean time from the defined end of the outbreak to the month it was counted by the health jurisdiction as a new TB case was 23 months (Standard deviation = 14 months). Blacks represented the highest proportion of cases (65%), with no significant difference between outbreak and post-outbreak cases (Table). Forty-eight percent (48%) of outbreak cases, compared with 62% of post-outbreak, had acid-fast bacilli (AFB) sputum smear-positive disease (p=0.04). More of the post-outbreak cases were in males (69% of outbreak cases versus 85% post-outbreak, p<0.01), or in persons who reported injection drug use (4% versus 11%, p=0.04) or had a history of homelessness (38% versus 51%, p=0.05) within the past year, or were foreign-born (3% versus 11%, p=0.02). All foreign-born cases were in persons who had resided in the United States for ≥2 years at time of diagnosis.

Epidemiologically linked versus nonlinked post-outbreak cases

Information on epidemiologic links for post-outbreak cases was available for five of the six outbreaks. These five outbreaks encompassed 89 post-outbreak cases: 39 epidemiologically linked and 50 not able to be linked to the original outbreak (i.e., nonlinked). The mean time from outbreak investigation to diagnostic verification did not differ between epidemiologically linked and nonlinked cases (24 versus 25 months, p=0.80). A high proportion of post-outbreak cases epidemiologically linked to the initial outbreak were in black males aged 25–44 years (66%), or in persons who were homeless (51%) or who self-reported excess alcohol use within the past year (49%). Seventy-two percent (72%) of epidemiologically linked cases had AFB sputum smear-positive disease versus 60% of nonlinked cases (p=0.25), and the majority of both groups had pulmonary TB (87% versus 78%, p=0.26). Among the nonlinked, a high proportion were black (60%), male (90%), or had a history of homelessness (42%) or excess alcohol use (54%) within the prior year. A difference between epidemiologically linked and nonlinked was observed in mean age (39 and 47 respectively, p<0.01, standard deviation for both groups 11.2). Additionally, epidemiologically linked cases were significantly more likely than nonlinked cases to have reported a history of injection drug use (18% versus 4%, p=0.04), and noninjection drug use (44% versus 18%, p<0.01) within the past year.

CONCLUSION

The utility of genotyping during outbreak investigation is well established, and the results of our study suggest that genotyping remains an important tool after outbreak investigations. In general, TB outbreak cases in this study had similar characteristics to post-outbreak cases diagnosed up to 4 years later. This similarity suggests that newly diagnosed TB cases with a matching genotype subsequent to an outbreak and in the same area are associated with that outbreak and therefore warrant further investigation.

The higher proportion of outbreak cases than non-outbreak cases with genotyping results is a result potentially driven by the utility of genotyping during an outbreak investigation to confirm relationships among culture-confirmed TB cases with suspected epidemiologic links. There were other limitations of this analysis. As CDC assistance is often requested for

complex investigations, the outbreaks presented here are not necessarily representative of outbreaks routinely investigated by state and local TB control programs. Other limitations included the limited time for follow-up of post-outbreak cases for the 2006–2007 outbreaks, the potential ecological issues associated with aggregating data from different geographic areas, and the potential under-representation of epidemiologically linked cases diagnosed in neighboring counties.

Of those characteristics with a significant difference, the proportion sputum smear-positive were likely higher in the post-outbreak group because all cases in that group were culture-positive, while the outbreak group included cases diagnosed by clinical criteria such as positive tuberculin skin test and abnormal chest radiograph in the absence of positive culture for *M. tuberculosis*.[6]

TB outbreak investigations are resource-intensive and time-consuming, and monitoring the effectiveness of control measures is critical. New tools such as TB GIMS have the potential to facilitate post-outbreak TB disease monitoring by making genotyping results readily available to state and local health jurisdictions within a relatively short period of time.

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Table

Characteristics of Outbreak versus Post-outbreak TB Cases in Six U.S. Outbreaks, 2003–2008

Characteristic	**Outbreak cases N = 111**		**Post-outbreak cases N = 110**		**P Value***
Mean age — years	43		44		0.41
Median age — years	43		46		0.70
Age Group, n (%)**					0.28
0–4	1	(1)	0		–
5–14	2	(2)	0		–
15–24	12	(11)	9	(8)	–
25–44	44	(39)	42	(38)	–
45–64	45	(41)	56	(51)	–
65+	7	(6)	3	(3)	–
Gender — male n (%)	77	(69)	93	(85)	0.007
Race/ethnicity, n (%)**					0.35
Hispanic	4	(4)	10	(9)	–
American Indian	14	(13)	10	(9)	–
Black	74	(67)	70	(64)	–
Native Hawaiian	0		1	(1)	–
White	19	(17)	18	(16)	–
Unknown	0		1	(1)	–
Foreign-born n (%)	3	(3)	12	(11)	0.02
HIV positive n (%)	15	(14)	22	(20)	0.20
Homeless within past year n (%)	42	(38)	56	(51)	0.05
Resident of correctional facility at diagnosis n (%)	10	(9)	5	(5)	0.29
Injection drug use within last year n (%)	4	(4)	12	(11)	0.04
Noninjection drug use within last year n (%)	23	(21)	32	(29)	0.15
Excess alcohol use within past year n (%)	48	(43)	51	(46)	0.64
Previous TB diagnosis n (%)	4	(4)	10	(9)	0.11
Pulmonary TB, n (%)	96	(87)	89	(81)	0.10

Characteristic	Outbreak cases N = 111		Post-outbreak cases N = 110		P Value*
Sputum smear positive n (%)	53	(48)	69	(62)	0.04
Cavitary disease n (%)	30	(27)	33	(30)	0.62
Any drug resistance n (%)	1	(1)	1	(1)	1.00

* P value determined by Pearson's chi-square test, or Fisher's exact test when cell sizes less than 5, for categorical comparisons, and by t-test or nonparametric Wilcoxon test for continuous variables

** Total percent might not equal 100% due to rounding

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